Neoadjuvant therapy before surgical treatment

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Neoadjuvant treatment in terms of preoperative radiotherapy reduces local recurrence in rectal cancer, but this improvement has little if any impact on overall survival. Currently performed optimal quality-controlled total mesorectal excision (TME) surgery for patients in the trial setting can be associated with very low local recurrence rates of less than 10% whether the patients receive radiotherapy or not. Hence metastatic disease is now the predominant issue. The concept of neoadjuvant chemotherapy (NACT) is a potentially attractive additional or alternative strategy to radiotherapy to deal with metastases. However, randomised phase III trials, evaluating the addition of oxaliplatin at low doses plus preoperative fluoropyrimidine-based chemoradiotherapy (CRT), have in the main failed to show a significant improvement on early pathological response, with the exception of the German CAO/ARO/AIO-04 study. The integration of biologically targeted agents into preoperative CRT has also not fulfilled expectations. The addition of cetuximab appears to achieve relatively low rates of pathological complete responses, and the addition of bevacizumab has raised concerns for excess surgical morbidity. As an alternative to concurrent chemoradiation (which delivers only 5–6 weeks of chemotherapy), potential options include an induction component of 6–12 weeks of NACT prior to radiotherapy or chemoradiation, or the addition of chemotherapy after short-course preoperative radiotherapy (SCPRT) or chemoradiation (defined as consolidation chemotherapy) which utilises the "dead space" of the interval between the end of chemoradiation and surgery, or delivering chemotherapy alone without any radiotherapy.

1. Rectal cancer: neoadjuvant therapy before surgical treatment

Rectal cancer is a very heterogeneous disease with different prognostic implications and varying outcomes. Historically, a high local recurrence rate has dominated decision-making. The need for radiation treatment has become deeply ingrained in surgical and radiation oncology culture, prompted by an imperative to avoid local pelvic recurrence at all costs. Local recurrence can be associated with intractable pelvic pain, tenesmus, mucinous discharge and intestinal obstruction, and few patients can be saved [1]. However, recent data suggest that metastases are now the predominant problem [2]. In a pooled analysis of 2795 patients recruited in five European randomised controlled trials, the 5-year distant metastasis rate was 30.8% [3].

Initially, because of the lack of reliable preoperative imaging, attempts to improve outcomes centred on postoperative chemoradiation according to pathological staging. With the emergence of more sophisticated imaging, this strategy has been extrapolated to the neoadjuvant arena, and validated by further phase III trials. Management has therefore moved from a solely surgically treated disease to the current widespread use of neoadjuvant radiation or combined chemotherapy and radiation therapy.

Over the past 3 decades the neoadjuvant management philosophy has also evolved independently in different regions of the world. The individual phase III studies performed

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in each country have driven the precise patterns of care. In the United Kingdom refinements in surgical technique – i.e. total mesorectal excision (TME) and extralevator abdominoperineal excision (ELAPE) [4,5] coupled with improvements in the quality of such surgery [6] – and the use of MRI and universal multidisciplinary team (MDT) discussion, have ensured that isolated local recurrence is now a rare event in 2012, if the surgeon can perform a good quality TME, even without radiotherapy [6]. However, even with expertly performed TME, the rate of distant recurrence has been documented as 18% in stage II patients and 37% in stage III patients in one important retrospective series [7].

Recently there has been enthusiasm for integrating more active systemic chemotherapy to increase down-staging and response and to lessen the risk of metastatic disease. In stage III colon cancer adjuvant chemotherapy based on 5-fluorouracil (5FU) reduced the risk of recurrence and prolonged survival, and hence has been firmly established and recommended as adjuvant treatment in patients following a curative resection [8]. More recent studies have confirmed that the addition of oxaliplatin to 5FU-based chemotherapy improves disease-free survival (DFS) [9,10] and overall survival (OS) [10] in patients with stage III colon cancer (although rectal cancers within 12 cm of the anal verge were excluded from these studies). FOLFOX is now considered an international standard as adjuvant chemotherapy for colon cancer in stage III disease, although there is still controversy regarding its use in high-risk stage II colon cancer. Yet the role of adjuvant chemotherapy in rectal cancer is not as clear-cut as in stage II and stage III colon cancer, and the validity of this standard has been questioned in a recent meta-analysis [11].

In Northern Europe short-course preoperative radiation therapy (SCPRT) (25 Gy in five fractions) followed by immediate surgery was evaluated as an adjunct to surgery [12,13]. Early trials showed an improvement in survival [12], and there have been subsequent consistent reports of lower local recurrence rates in randomised trials [14,15]. Yet integration into routine practice in other parts of the world has always been slightly tempered by early reports of severe acute and long-term toxicity [12,13,16].

When directly compared with standard chemoradiotherapy (CRT), SCPRT shows similar efficacy [17,18]. The recent TROG 01.04 trial in clinical stage T3 rectal cancer compared SCPRT with long-course preoperative CRT [18]. The trial confirmed similar outcomes for SCPRT and CRT for distant recurrence, overall survival and late effects. After a minimum follow-up period of 3 years cumulative incidences of local recurrence at 5 years were 7.5% for SCPRT and 5.7% for CRT respectively ($P = 0.51$). For distal tumours, six of 48 SCPRT patients and one of 31 CRT patients had a local recurrence ($P = 0.21$).

In the landmark German l CAO/ARO/AIO – 94 Trial [19] a total of 823 patients were randomised between preoperative CRT and postoperative CRT (patients received postoperative adjuvant chemotherapy in both arms of this trial). Acute and late toxicities were significantly reduced with the preoperative approach, although it should be recognised that a higher radiation dose was mandated for the postoperative regimen. Loco-regional failure was only 6% in the preoperative arm versus 13% in the postoperative arm. There was, however, no difference observed in the distant metastases rate, DFS or OS. This advantage is also supported to some extent by the National Surgical Adjuvant Breast and Bowel Project (NSABP R-03) trial results [20] which showed a statistically significant improvement in 5-year DFS (65% versus 53%, $P = 0.011$) for preoperative therapy (although it included an additional 6 weeks of neoadjuvant chemotherapy). Both trials have therefore served to validate the benefit of neoadjuvant 5FU-based chemoradiotherapy for locally advanced rectal cancer compared with postoperative therapy.

Hence, randomised controlled trials have unequivocally demonstrated that preoperative radiotherapy or chemoradiation [12,13,20–23] is more effective than postoperative chemoradiation therapy in terms of reducing local recurrence, and with less acute and late toxicity than postoperative therapy. Yet the risk of dying from rectal cancer is linked mainly to the development of distant metastases, and to experience a late local recurrence as described by Sauer et al. [23] the patient needs to survive 5 years. As an alternative setting to concurrent chemoradiation (which only delivers 5–6 weeks of chemotherapy), potential options are an induction component of 6–12 weeks of neoadjuvant chemotherapy (NACT) prior to radiotherapy or chemoradiation [20,24–27], adding chemotherapy after SCPRT or chemoradiation (defined as consolidation chemotherapy) which utilises the "dead space" of the interval between the end of chemoradiation and surgery [28–30], or delivering chemotherapy alone without any radiotherapy [31,32].

In Valentini's recent pooled analysis of seven chemoradiation trials, the most effective predictive model for developing local recurrence was based on ypT stage, cT stage, age, ypN stage and concomitant delivery of adjuvant chemotherapy. Hence the only preoperative data available were age and cT status. The best model for predicting distant metastases used ypN stage, ypT stage, surgical procedure and delivery of adjuvant chemotherapy (in order of relevance). Hence these nomograms are unhelpful in the preoperative setting [3].

More recently, outcomes have been shown to vary according to predicted (i.e. clinical) T stage of disease (Table 1), and other prognostic factors (mainly extramural vascular invasion and tumour extent in relationship to the circumferential resection margin), which can be determined by preoperative magnetic resonance imaging (MRI). Hence a more individualised approach to treatment selection is now feasible according to the relative risk of local recurrence versus metastatic disease. However, the consistently accurate parallels between clinical imaging and pathological staging obtained in the MERCURY study have not been easily reproduced. Both the technical aspects and the immediate demands of the presence of a specialist radiologist for optimal MRI imaging, and the interpretation of the scans, mean there is a significant degree of individual variation between and within centres. All of these factors have contributed to a variable acceptance of the technique worldwide.

In this article for the ESMO educational symposium we discuss the various available options for neoadjuvant therapy, their rationale and the results obtained. We consider the different approaches of long-course CRT and SCPRT: the intensi-

Table 1 – Japanese-style surgery with laparoscopic pelvic lymph-node dissection (LPLND). Risk of local recurrence and distant metastases. Cut-off for depth of mesorectal involvement ⩽4 mm.

			Stage IIA	Stage IIIB	All Stage III
⩽4 mm	Local recurrence		12/295 (4.1%)	14/204 (6.9%)	21/245 (8.6%)
		Distant metastases	21/295 (7.1%)	36/204 (17.6%)	47/245 (19.2%)
>4 mm	Local recurrence		13/295 (7.7%)	23/218 (10.6%)	34/267 (12.7%)
		Distant metastases	28/168 (16.7%)	58/218 (26.6%)	75/267 (28.1%)

fication of preoperative radiation and chemoradiation with dose-escalation of external-beam radiotherapy (EBRT), using brachytherapy, intraoperative radiotherapy (IORT), hyperfractionation and various available techniques such as intensity-modulated radiotherapy (IMRT). We make recommendations as to which clinical or imaging features require preoperative CRT or SCPRT to be delivered, and where it could possibly be avoided. The strategies of neoadjuvant, concurrent, consolidation (i.e. immediately following chemoradiation and prior to surgery) chemotherapy with cytotoxic agents are explored. We speculate on the initial attempts to integrate biological agents as future potential strategies of treatment with and separate from radiation.

The current era of precision imaging offers many options for conformal external-beam radiotherapy, such as IMRT, volumetric arc therapy (VMAT), brachytherapy and a plethora of systemically active cytotoxic and biological agents. Practice has also been driven more recently by meticulous refinements in surgical technique, in which all the surrounding mesorectal fat are removed in a neat anatomical package (total mesorectal excision and extralevator abdominoperineal excision), the availability and quality of preoperative MRI to determine potential risks, an increasing value placed on histopathology and assessments/metrics of the quality of surgery. TME is associated with much lower rates of local recurrence and improved survival [4], but all these advances have contained and driven down the local recurrence rate.

In 2005, investigators from Hong Kong challenged the accepted wisdom and questioned whether low-risk stage II patients benefit from neoadjuvant therapy [33]. With a median follow up of 43 months, they reported a 6% local recurrence rate at 5 years for patients undergoing anterior resection (with a median level of tumour at 8 cm from the anal verge). Recent population-based data [34] and retrospective series exploiting these advances further undermine the approach of a blanket use of radiotherapy/chemoradiation by exploring the omission of radiotherapy when MRI suggests the tumour is easily resectable and the circumferential resection margin (CRM) is not threatened [35–38]. Others have also recently questioned the routine use of chemoradiation for rectal cancer [39,40].

The current high clinical and pathological response rates [41] observed from chemotherapy in small clinical trials also offer an alternative option to chemoradiation. So the rationale for selecting patients suitable and appropriate for neoadjuvant preoperative radiotherapy/chemoradiotherapy needs reconsidering.

For patients with resectable rectal cancer prior to the current TME era, trials of CRT or SCPRT demonstrate a reduction in loco-regional failure (LRF), but without extending DFS or OS.

More recent randomised trials in locally advanced rectal cancer (LARC) suggest that the high historical local recurrence rate of the 1990s has been reduced to <10% with CRT and/or SCPRT. In the main, local recurrence in rectal cancer has been replaced by an even larger risk of metastatic disease as the current predominant problem. Hence many oncologists have recommended both intensifying chemotherapy in the neoadjuvant setting, and also integrating other cytotoxic drugs, in addition to 5FU, into CRT schedules as the logical next steps to improve outcome in rectal cancer.

In the UK and Northern Europe patients with rectal cancer are selected for preoperative treatment on the basis of clinical staging. Many multidisciplinary teams categorise patients into “the good, the bad and the ugly“, which allows the definition of three different clinical settings for rectal cancer [42]. Early cT1/T2 tumours are not usually treated with radiotherapy; more advanced T3 tumours in which the patient is considered at risk of local recurrence [15,43] are advised to receive SCPRT followed by TME; and thirdly patients, with clinically unresectable cancers – where MRI suggests a threatened/ breached CRM (10–15% of cases), or the levators are potentially involved, or in cancers which require surgical resection beyond the conventional TME plane – then radiation as a component of CRT is clearly necessary for down-staging.

MRI assessment forms the basis of the recent UK 2011 NICE clinical colorectal guidelines on colorectal cancer (http://guidance.nice.org.uk/CG/Wave16/2) which defines three different risk groups of patients with rectal cancer, according to the risk of local recurrence. MRI is sufficiently sophisticated to allow accurate prediction of mesorectal surgical margin involvement by tumour (within a tolerance of 1 mm) preoperatively, and can also demonstrate macroscopic extramural vascular invasion (EMVI). Both a positive CRM and EMVI carry a high risk of subsequent metastatic disease.

Few patients in any of the randomised phase III studies had standardised staging with MRI. Few had primary rectal cancers staged as T4 or, by MRI criteria, were encroaching on, or extending beyond total mesorectal excision planes, which are considered to require preoperative chemoradiation (and sometimes surgical resection beyond conventional TME planes). Such poor-prognosis patients have an even higher risk of metastatic disease even after successful surgery.

2. Radiotherapy as neoadjuvant treatment

2.1. SCPRT

Several trials with more than 6000 patients support the benefit of SCPRT in reducing local recurrence. The rationale for SCPRT is based on the short overall treatment time (OTT), which allows surgery to take place before the radiation reaction is expressed, but does not allow sufficient time for tumour shrinkage.

The Swedish Rectal Cancer Trial [13] randomly assigned patients with cT1–3 rectal cancer to SCPRT and immediate surgery versus surgery alone (not TME). A significant improvement in both local recurrence and survival was observed in the SCPRT arm. The Dutch group performed the Commissie Klinisch Vergelijkend Onderzoek (CKVO) 95-04 trial, which used the same design but trained and mandated surgeons to perform TME. Both early [43] and more mature long-term reports [44] confirmed a significant improvement in local control with SCPRT, although no difference in overall survival was observed.

The MRC CR07 trial [6,15] randomised 1350 rectal cancer patients to either SCPRT (5×5 Gy) followed by immediate surgery or selective postoperative chemoradiation (25×1.8 Gy with concurrent 5-fluorouracil) administered only for patients with histologically involved ($\leqslant$1 mm) resection margins. The majority of resections were considered TME, but only 51% were good quality TME in the mesorectal plane [6]. Overall, clinically significant absolute risk reduction in the 3-year local recurrence rate of 6.2% was observed (4.4% for SCPRT versus 10.6% for selective postoperative CRT), corresponding to a relative risk reduction of 61%. At 3 years, disease-free survival was 6% better for SCPRT, but there was no improvement in overall survival. The CR07 trial suggests SCPRT reduces the risk of local recurrence for all tumour locations, all pathological stages, and good, average or poor quality surgery.

SCPRT may also only partially compensate for a positive CRM [45,46] if this threat to the mesorectal fascia (MRF) was not detected on preoperative MRI. This strategy has aims different from those of long-course CRT, where we hope to shrink/down-stage the tumour and facilitate an R0 resection to be performed, or to increase the chances of performing sphincter-sparing surgery.

Other advantages of SCPRT include high compliance, even in the elderly, and low cost. Two large randomised trials have each reported that in resectable cancers, SCPRT and CRT are equivalent in terms of outcomes such as local recurrence, disease-free survival (DFS) overall survival (OS) and toxicity [16,17] (Table 2). In the UK, SCPRT is increasingly being used with an interval to surgery or as a radical treatment ± high dose rate brachytherapy (HDRBT). SCPRT is considered to have the advantage of rapid delivery and high compliance for patients who are frail, elderly and with cardiac and renal co-morbidities which preclude 5FU-based chemotherapy.

However, there is a price to pay. Long-term data from randomised trials of SCPRT versus surgery alone demonstrate almost twice the prevalence of bowel dysfunction after SCPRT [47–50]. The CR07 data suggest that SCPRT caused a significant increase in unintentional release of stools [51]. More recent retrospective analyses suggest that frequency, urgency, evacuatory difficulties and faecal incontinence – i.e. the low anterior resection syndrome (LARS) – are common. Effects on sexual functioning [52] and urinary incontinence [49] have also been documented after SCPRT.

With modern MRI, metabolic imaging with positron emission tomography/computed tomography (PET/CT) and individual biomarkers it should be possible to be more selective for risk of local recurrence. It is therefore difficult to support the current widespread advocacy for routine adjuvant radiotherapy as used in the treatment arms of recent trials. Alternatively for this same reason, efforts have been made to limit the radiation dose to normal rectum.

The histology is only minimally corrupted by the radiotherapy changes, allowing accurate pathological staging in terms of the nodal status, extramural vascular invasion and perineural invasion. Patients treated with SCPRT or HDRBT will undergo surgical resection and receive postoperative adjuvant chemotherapy many weeks earlier than with conventional CRT. Hence selection for and delivery of postoperative adjuvant chemotherapy with systemically active schedules (e.g. FOLFOX) can usually start within 6–10 weeks of diagnosis.

2.2. SCPRT and surgery after an interval

Two retrospective studies [53,54] reported safety and efficacy of SCPRT with an interval of several weeks to allow response. Both reported similar curative resection rates and local control as after preoperative long-course CRT. Although the populations of these studies varied, a pathological complete response (pCR) was observed in 4/37 patients (11%) and 2/24 patients (8%), respectively, who underwent surgery after an interval of a few weeks.

A randomised Polish study of 154 patients with locally advanced rectal cancer who were operated using TME between 1999 and 2006 examined the influence of the time interval between SCPRT and surgery on long-term OS and recurrence rate [55]. Patients were randomised between SCPRT (5×5 Gy) followed by surgery either 7–10 days or 4–5 weeks later after completion of RT [55]. With approximately 4 years minimum follow-up, 5-year survival rates were 63% and 73% for immediate and later surgery respectively ($P = 0.24$). The longer time interval between RT and surgery resulted in a greater down-staging rate (44.2% versus 13%), but did not increase sphincter-saving procedures or curative resections.

A further small randomised trial of 83 patients with resectable (stage II and III) rectal cancer [56] compared the clinical and pathological down-staging from SCPRT and long-course CRT followed by surgery after an interval of 6 weeks in both groups. The preliminary results suggested improved tumour down-sizing from CRT compared to SCPRT. Pathological complete response was observed in one patient (2.7%) in the SCPRT group versus six patients (13.1%) in the CRT group. Postoperative morbidity and R0 resection rates were similar. The ongoing Stockholm III trial – which is randomising between three arms: SCPRT proceeding to immediate surgery within a week, SCPRT and delayed surgery after 4–8 weeks, and 50 Gy in 25 fractions with surgery after a similar interval

Table 2 – Trials comparing shortcourse preoperative radiotherapy (5X5 Gy) with preoperative chemoradiation.

Trial	No	Stage	chemo	Adjuvant chemotherapy	Local recurrence	RFS/DFS	5 year OS
Polish SCPRT	155	cT3-T4	none	Optional	Crude 9%	4 year DFS 58%	4 year OS 67%
Polish CRT	157	cT3-T4	5FU/FA	Optional	Crude 14%	4 year DFS 56%	4 year OS 66%
TROG SCPRT	163	II-III	none	Mandated FUFA 6/12	3 years 7.5%	5 year RFS 64%	5 year 74%
TROG SCPRT	163	II-III	PVI 5FU 225mg/m2	Mandated FUFA 4/12	3 years 4.4%	5 year RFS 61%	5 year 70%
Latkauskas SCPRT	37	II-III	none	Not stated	Not stated	Not stated	Not stated
Latkauskas CRT	46	II-III	5FU/FA	Not stated	Not stated	Not stated	Not stated
Pach 2012 SCPRT immediate 7-10 days	77	I-III	none	Not stated	1.5%	Not stated	63%
Pach 2012 SCPRT delayed 4-5 weeks	77	I-III	none	Not stated	7%	Not stated	73%

SCPRT = short course preoperative radiotherapy; CRT = chemoradiation; RFS/DFS relapse free survival/disease free survival; OS = overall survival; FUFA = 5FU and folinic acid.

[57] – will also provide additional information on allowing an interval for response after SCPRT. However, current data suggest that it is feasible to use SCPRT and delay for several weeks, opening the opportunity to fill this gap with chemotherapy. This strategy has been successfully employed in patients with synchronous metastases [58].

2.3. *Chemoradiation*

The rationale for long-course chemoradiation is to achieve additive effects from the combination of chemotherapy and radiation, both locally and systemically, with a concurrent fluoropyrimidine, thereby inducing down-staging/downsizing, and in some cases facilitating sphincter-sparing procedures, while at the same time reducing distant metastases and in a small group of patients (approximately 10–15%) achieving tumour sterilisation. The current shortcoming of this approach is that we have only managed to integrate single-agent fluoropyrimidines (intravenous 5FU or capecitabine/UFT) at suboptimal, sub-systemic doses into everyday practice.

In ultrasound-staged resectable cancers (i.e. presumably where the preoperative MRI would now suggest the CRM/MRF is not potentially involved), or where down-staging is not required, then SCPRT and CRT have been shown to be equivalent in terms of outcomes such as local recurrence, DFS and OS [17,18]. For more advanced cases, where the surgeon assesses the tumour as unresectable and/or the CRM/MRF is recognised to have been breached or threatened according to the MRI appearances, long-course CRT with the addition of 5FU to radiation has favourable effects on relapse-free survival (RFS) and cancer-specific survival with a trend to improve overall survival [59].

Concerns also remain that the delivery of adjuvant chemotherapy in the postoperative setting has frequently been compromised by delays because of surgical morbidity, slow recovery and healing, poor tolerance, and marked dose reductions, with patient compliance being approximately 50% [19,60,61]. These three studies showed that 20%, 23% and 25%, respectively, failed to start postoperative 5FU-based adjuvant chemotherapy. The observation from Biagi et al. [62] that even a few weeks delay following curative surgery before implementing systemic chemotherapy impacts on survival provides a rationale to administer chemotherapy preoperatively.

Despite the above controversies, consensus guidelines from European groups [63,64], Canada [65] and the United States of America [66] recommend preoperative chemoradiation for the majority of patients with stage II and stage III rectal cancer. This approach has narrowed to the conventional use of 45–50.4 Gy at 1.8 Gy per fraction, irrespective of the stage, size, site and molecular biology of the cancer [67].

There are also significant long-term late effects, including an increased risk of insufficiency fractures in the pelvis [68,69], and an increased risk of second malignancies from CRT even within 10–12 years. Tubiana [70] warns that large target volumes treated with moderate doses carry a high risk of second malignancy. The incidence of second malignancy has probably been underestimated because, with a median age of 65–70 years, patients in rectal cancer trials had a relatively short life-expectancy after treatment, and follow-up is usually short. With recent gains in survival, longer follow-up, cancer registries and end-result programmes, the cumulative incidence of second malignancies could reach as much as 20% of patients treated by radiotherapy [70].

2.4. *Intensity-modulated radiotherapy (IMRT)*

Clinical trials of SCPRT or CRT have almost invariably used three- or four-field techniques. Acute gastrointestinal toxicity is the commonest dose-limiting toxicity in many chemoradiation trials, and provides the main dose-limiting factor for the radiotherapy. In the German CAO/ARO/AIO-94 trial, preoperative chemoradiation led to a 12% rate of G3–4 acute toxicity in terms of diarrhoea, and a 9% rate of gastrointestinal G3–4 late toxicity. Total doses of between 45 and 50 Gy probably lead to a 5% risk of late toxicity for the small bowel at 5 years, and there is a significant association between $\leqslant$G3 acute small bowel toxicity and the volume of small bowel irradiated [71–74]. Acute toxicity in trials which have integrated oxaliplatin have even higher rates of G3/G4 diarrhoea at approximately 25%, and might be expected to be associated with a greater risk of late damage to the small bowel. None of the randomised phase III trials to date in rectal cancer have used IMRT.

Highly conformal planning using multi-leaf collimators (MLCs) which can be adjusted during the treatment may limit the radiation dose to the bowel and other normal structures, thereby potentially reducing acute and late gastrointestinal side effects [75–77]. A recent retrospective review demonstrated a significant decrease in gastrointestinal toxicity grade $\geqslant 2$ for patients receiving IMRT [78]. We clearly need to evaluate the precise mechanisms that are responsible for the late functional effects of radiotherapy, as some patients could either forego radiotherapy completely, or the radiotherapy fields could be more tailored to avoid say the lumbarsacral plexus or the sphincter mechanisms themselves.

Alternatively, IMRT/IGRT may facilitate EBRT dose-escalation of radiotherapy protocols and more aggressive combinations of radiotherapy with cytotoxic chemotherapy and/or novel systemic agents. The downside is increased low-dose exposure of the surrounding healthy tissue circumferentially around the tumour, potentially leading to an increase in the volume of normal tissues exposed to low doses of radiation. IMRT with capecitabine and oxaliplatin is being tested in a phase II study (RTOG 08-22) for cT3-4N0-2 patients with rectal cancer. The preliminary results, presented in abstract form only, appear to show that IMRT is feasible with a high rate of contouring and planning compliance and less gastrointestinal grade $\geqslant 2$ toxicity compared with other RTOG rectal cancer chemoradiation studies such as RTOG 0247 [79].

More recently several other strategies have been used to increase the radiation dose to the primary with brachytherapy or contact boost, with intraoperative radiotherapy using electrons.

3. Brachytherapy

High-dose-rate intraluminal brachytherapy (HDRBT) is highly conformal; the rapid fall-off in dose allows a high dose of radiation to be delivered at the mucosal surface of the rectum overlying the tumour and reduces doses to surrounding normal structures compared to conventional radiotherapy techniques. Publications are sparse for resectable rectal cancer, and rely mainly on a single institution (McGill University in Montreal) which has reported significant tumour regression in over 300 patients, over 29% of the patients achieving a complete pathological response at surgery [80–82]. Because of the rapid dose fall-off, HDBRT may treat the pelvic lymph nodes less adequately. Preoperative HDRBT (26 Gy over 4 days) followed by surgery after 4–8 weeks compares favourably in terms of complications and outcomes with SCPRT in a recent matched retrospective analysis from Canada and Sweden [83]. Brachytherapy also appears as effective as long-course conventional CRT but may be associated with less severe acute toxicity. However, many radiation oncologists remain uncertain about the late sequelae from use of higher dose rates.

There is a significant dose–response relationship for tumour regression after preoperative CRT [84]. Recent reports describe a 31% pCR and 83% achieving an R0 resection in 34 patients treated with 10 Gy HDRBT boost following downstaging of potentially resectable rectal cancers with long-course chemoradiotherapy [85]. For inoperable tumours, HDBRT has been used to dose-escalate after chemoradiation to achieve a greater tumour response and facilitate a curative resection [86]. A small randomised study (Lyon 96–02) suggests that a higher dose achieves a higher rate of complete clinical response, and hence increases the chance of sphincter preservation from 44% to 76% [87,88].

4. Integration of cytotoxic agents into the neoadjuvant setting

The intentions of integrating oxaliplatin into the multimodality treatment are, first, to assess additional effects from preoperative neoadjuvant using oxaliplatin as a radiosensitiser, to achieve greater tumour response, and to reproduce some of the gains in survival achieved by cisplatin in chemoradiation schedules in cervix cancer/head and neck cancer. Second, the hope is to achieve systemic effects, since in metastatic disease the addition of oxaliplatin to the combination of 5FU and folinic acid (FOLFOX) offers response rates in the range of 50% [89]. Oxaliplatin also has a proven role in the adjuvant setting in CRC.

There are two distinct philosophical approaches for integrating oxaliplatin in rectal cancer. Radiation oncologists aim to integrate oxaliplatin during radiotherapy as a radiosensitiser to increase response (usually at sub-systemic doses for tolerability). In contrast, medical oncologists are designing phase II/randomised phase II trials using systemically active high-dose chemotherapy outside chemoradiation to reduce micrometastases outside the pelvis.

Four randomised phase III studies – Action Clinique Coordonnées en Cancérologie Digestive (ACCORD), STAR-01 and NSABP R04 and CAO/ARO/AIO-04 and PETACC-6 studies – (Table 3) have compared preoperative chemoradiotherapy using a combination of a fluoropyrimidine and oxaliplatin with preoperative chemoradiotherapy using an intravenous or oral fluoropyrimidine alone [91–95]. Early results from these randomised phase III trials have not shown any significant impact on early pathological response with the exception of the German CAO/ARO/AIO-04 study.

The ACCORD trial, which compared capecitabine plus oxaliplatin with capecitabine alone, showed no difference in the pCR rate, which (unusually for a phase III) formed the primary end-point (19.2% versus 13.9%, $P = 0.09$) [92,93]. The STAR-01 trial also showed no difference in the pCR rate (15% versus 16%, $P = 0.982$.). Yet the percentage of patients with pathological M stage was significantly lower in the 5FU-plus-oxaliplatin group (2% versus 11%, $P = 0.014$), suggesting that addition of oxaliplatin to preoperative CRT might have influenced the development of distant metastases. In contrast, the CAO/ARO/AIO-04 study showed an improved pCR rate in patients receiving oxaliplatin (17% versus 13%, $P = 0.038$) [96]. In addition, the PETACC-6 trial randomised patients between preoperative RT (50.4 Gray in 25 fractions) with capecitabine alone and the same radiation schedule with capecitabine + oxaliplatin (50 mg/m^2). The trial has completed accrual and results are awaited.

4.1. *Irinotecan*

Several phase II trials have suggested a potential benefit for the addition of irinotecan to preoperative CRT. The random-

Table 3 – Short-term outcomes from randomised studies integrating oxaliplatin (OXA) as radiosensitiser.

outcomes	STAR-01		ACCORD- 0405		CAO/ARO/AIO-04		NSABP R04		PETACC-6[a]	
	5FU379	OXA352	Cape293	OXA291	5FU624	OXA613	5FU/cape622	OXA631	5FU/cape547	OXA547
G3/G4 diarrhoea	4%	15%	3%	13%	8%	12%	7%	15%	Not stated	Not stated
ypCR	16%	16%	14%	19%	13%	17%	19%	21%	11%	13%
Ypn0	74%	71%	70%	72%	70%	72%	Not stated	Not stated	Not stated	Not stated
Ypn+	26%	29%	30%	28%	30%	28%	Not stated	Not stated	Not stated	Not stated
CRM <1mm	7%	4%	13%	8%	6%	5%	Not stated	Not stated	Not stated	Not stated
R0 resection	94%	97%	Not stated	Not stated	92%	90%	Not stated	Not stated	92%	86%

5FU, 5-fluorouracil; CRM, circumferential resection margin.
[a] Ref. [90]

ised phase II RTOG-0012 trial showed no benefit [97,98]. The current national trial in the UK (ARISTOTLE) is examining the utility of the incorporation of irinotecan into preoperative CRT in MRI-defined unresectable/borderline resectable rectal cancer (www.controlled-trials.com/ISRCTN09351447).

4.2. *Integration of biologicals*

Standard chemotherapy regimens for CRC have integrated molecularly targeted agents (cetuximab, panitumumab, bevacizumab and aflibercept) to improve response rates or extend PFS and OS. The approach of using epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) inhibitors has been extrapolated to the treatment of locally advanced rectal cancer to avoid overlapping toxicities. Yet the reader should be mindful that there is only a single phase III study in any disease site demonstrating an advantage to combined biological agents and radiotherapy compared with radiation alone [99]. Also these agents have not been shown to have activity in the adjuvant setting [100,101].

Bevacizumab added to standard cytotoxic chemotherapy is associated with improved survival and higher pathological response rates in patients undergoing resection of colorectal liver metastases [102], but may not affect response rates defined by RECIST (response evaluation criteria in solid tumours) [103]. Bevacizumab may be safely administered in the preoperative setting for the treatment of liver metastases [104], without increasing post-surgical complications [105,106].

A phase I clinical study of bevacizumab prior to and concurrently with 5FU-based CRT reduced tumour perfusion, vascular volume, microvascular density, interstitial pressure and viable endothelial cells [107]. Willett and colleagues continued into a phase I/II study and reported a pCR rate of 16%, and an additional 72% of patients who had only microscopic foci remaining after treatment with bevacizumab and 5FU plus RT in patients with T3/T4 tumours [108].

In another small phase I study in patients with metastatic (four) or locally advanced rectal adenocarcinoma (seven), the combination of bevacizumab, oxaliplatin and capecitabine chemoradiation was active with a pCR of 22%, but with significant acute toxicity [109].

In a phase II study in patients with T3/4, N1, or recurrent disease, administration of capecitabine and bevacizumab concomitant with preoperative RT resulted in a pCR rate of 32% and a microscopic residual disease rate of 24% [110]. A slightly lower pCR rate of 24% was observed in a phase II study of patients with T3/4N0 or T1-4N1-3 rectal cancer who received induction CT comprising only two cycles of 5FU/LV + oxaliplatin (FOLFOX6) plus bevacizumab, followed by concomitant RT plus FOLFOX and bevacizumab [111]. In this study 9/25 patients (36%) also developed postoperative complications [111].

The more recent AVACROSS study selected 47 patients according to MRI criteria, and used four cycles of induction chemotherapy using capecitabine, oxaliplatin and bevacizumab, followed by chemoradiation with concurrent capecitabine and bevacizumab [112]. Results are impressive, with 98% having an R0 resection and 36% achieving a pCR, while a further 23% were down-staged to ypT1/T2N0. There was one sudden death during the induction, and surgical morbidity appears prominent, since 26/45 patients (58%) experienced at least one postoperative complication and 11/45 (24%) required surgical re-intervention (even though the median time from the last dose of bevacizumab to surgery was 2 months).

A phase II trial evaluated preoperative capecitabine, oxaliplatin and bevacizumab with radiation therapy followed by surgery and postoperative 5FU, leucovorin, oxaliplatin (FOLFOX) and bevacizumab for locally advanced rectal cancer in 57 patients [113]; 17% achieved a pCR, but 47% of patients who underwent surgery experienced a surgical complication. A Canadian study achieved a pCR of 18%, but four patients (11%) required re-operation due to complications [114].

A further study evaluating bevacizumab/chemoradiation in the preoperative and adjuvant settings in 66 patients with stage II/III rectal cancer [115] achieved a pCR rate of 29%, but again showed frequent grade 3/4 toxicity and surgical morbidity.

None of these studies showed a consistent definitive signal of improved efficacy. Yet, since the eligibility criteria in the AVACROSS study, which achieved a pCR of 36%, were similar to those of the GEMCAD study [116], where a pCR of only 14% was observed with induction Xelox and capecitabine and oxaliplatin chemoradiation, it is possible that the addition of bevacizumab offers greater efficacy. However, several studies raise concerns that the combination of bevacizumab and radiation may impact on surgical morbidity. Future studies need either to leave a longer interval following the completion of bevacizumab before surgery or to drop the bevacizumab from the chemoradiation component.

Preliminary results of chemoradiation clinical trials with cetuximab, on the early clinical endpoint of pCR, are at best

disappointing. A large multinational randomised phase II study EXPERT-C (NCT00383695) has compared neoadjuvant therapy comprising oxaliplatin, capecitabine and chemoradiotherapy with or without cetuximab in 164 patients.

Kras status (mutant or wild-type) does not appear to be predictive for pCR in rectal cancer when EGFR inhibitors are integrated into chemoradiation regimens [117,118]. In the more recent Expert C study, in the group of patients with wild-type Kras, who received capecitabine, oxaliplatin and cetuximab, the overall survival at 3 years was 96% [119].

5. Chemotherapy additional to SCPRT or CRT

As an alternative setting to concurrent chemoradiation (which only delivers 5–6 weeks of chemotherapy) potential options are either an induction component of 6–12 weeks of NACT prior to radiotherapy or chemoradiation [24–26], adding chemotherapy after SCPRT or chemoradiation as consolidation, which utilises the "dead space" of the interval between the end of chemoradiation and surgery [28,30], or delivering chemotherapy alone without any radiotherapy [31,32].

5.1. *Neoadjuvant/induction chemotherapy prior to chemoradiation*

The most popular method of integrating chemotherapy is as induction prior to chemoradiation, which achieves high rates of symptomatic improvement (65%) [120]. Clinical response rates with induction chemotherapy vary between 28% [120], 41% [27] and 59% [119] when cetuximab was added, with no patients observed to have progressive disease.

Phase II randomised studies [25,116,119,121] suggest that neoadjuvant chemotherapy prior to chemoradiation is feasible, and can be delivered with minimal compromise of either the radiation or subsequent surgery.

The EXPERT phase II study of 78 patients used a 12-week induction phase of capecitabine and oxaliplatin followed by chemoradiation with capecitabine with chemoradiation (total dose 54 Gy) in locally advanced rectal cancer. The radiological response rate was 81% (two CRs and 50% PRs). The early outcome results of this study appear impressive, but it is not possible to determine the relative contributions of the induction chemotherapy and the concurrent CRT schedule or the high dose of pelvic radiotherapy (54 Gy); however, when compared to the group's subsequent study, with an identical eligibility and chemotherapy schedule but a lower RT dose (50.4 Gy), the pCR fell from 23% to 14% [119]. Mature results of the EXPERT trial in 105 patients [25] demonstrated a 3-year PFS and OS of 68% and 83% respectively. The 3-year RFS for the 93 patients who had a R0 resection was 74%.

A Spanish study (GCR-3 study) compared a conventional schedule of chemoradiation followed by TME and postoperative adjuvant chemotherapy using capecitabine and oxaliplatin, against induction chemotherapy using capecitabine and oxaliplatin followed by CRT and TME [116]. The pCR rate was similar in both arms, 14% versus 13%, but significantly more patients in the postoperative adjuvant arm had grades 3/4 acute toxicity than in the induction arm (54% versus 19%; $P = 0.0004$, respectively). In the postoperative adjuvant arm, 25% of patients did not begin treatment, and only 51% received all four cycles, whereas 100% of patients in the induction arm began treatment, and 92% received all four ($P = 0.001$). The relative dose intensity for both capecitabine and oxaliplatin were significantly higher in the induction arm, with no differences in radiotherapy compliance between the two arms ($P = 0.001$). Despite the high compliance in the induction arm, 3-year DFS was not increased [121].

The NASBP-R-03 (National Surgical Adjuvant Breast and Bowel Project R-03) is the only phase III trial to have integrated neoadjuvant chemotherapy at systemic doses. The trial randomised 267 patients to either preoperative 5FU based CRT ($n = 130$) or postoperative CRT ($n = 137$) [20]. In addition, the preoperative arm utilised up-front weekly bolus 5FU/leucovorin (LV) for 6 weeks prior to starting concurrent CRT (5FU/LV for 5 days during the first and fifth weeks of radiation to a total dose of 45 Gy with a 5.4 Gy boost). Thus the trial mandated 3 months of neoadjuvant 5FU/LV in the preoperative arm, followed by postoperative adjuvant weekly 5FU/LV.

The accrual was lower than expected (267 of the planned 900 patients). The preoperative treatment arm failed to demonstrate an improvement in local recurrence. The 5-year cumulative incidence of locoregional recurrence was 10.7% for both treatment arms (HR = 0.86; 95%CI, 0.41–1.81; $P = 0.693$), but had a statistically improved DFS with a hazard ratio of 0.629 ($P = 0.011$) and a trend towards improved overall survival. These findings suggest an effect of the neoadjuvant chemotherapy on systemic disease.

In the CONTRE trial, patients received eight cycles of FOLFOX as NACT followed by CRT and surgery. Preliminary data presented at the Gastrointestinal American Society of Clinical Oncology (GI ASCO) 2013 meeting from the first 32 patients reported a 33% pCR rate and >90% compliance [122].

A recent study with induction FOLFOX and bevacizumab [111] provoked grade 3/4 toxicity during chemoradiation in 19 of 25 patients (76%). In some of these phase II studies the authors do not clearly report the toxicity profiles separately for concomitant chemoradiation and when used as full-dose chemotherapy alone [28]. However, studies of neoadjuvant chemotherapy raise concerns regarding the high rate of toxic deaths. Patients with the more advanced and larger pelvic tumours appear to have a particularly high risk of thromboembolic and cardiac effects [25,123], less so if T4 tumours are excluded [31].

5.2. *Consolidation chemotherapy (neoadjuvant chemotherapy following chemoradiation)*

Consolidation chemotherapy does not compromise compliance to and delivery of chemoradiation. Retrospective data from the Memorial Sloane Kettering Cancer Center [124] and others [125,126] suggest that increasing the interval between CRT and surgery might enhance the rate of pathological complete responses, although other studies partly contradict this [127,128].

Habr-Gama reported that extending the duration of the chemotherapy post-chemoradiation increased the complete clinical response rate (cCR) of 48%, achieving an overall complete response rate (i.e. including cCR and pCR) of 65% [27]. Recent studies have tested the hypothesis that by delaying

Table 4 – Phase II/phase III trials of neoadjuvant chemotherapy in progress.

Study	Preoperative treatment	Entry criteria	Status	RT/CRT	Comments
BACCHUS NCRI Randomised phase II (recruiting) 60 patients	FOLFOX + bevacizumab for 5 courses, then final FOLFOX, then surgery versus FOLFOXIRI bevacizumab for 5 courses ,then final FOLFOXIRI then surgery	MRI-defined entry	Yet to open	SCPRT or CRT only for progression/lack of response	Primary endpoint: pCR
RAPIDO Phase III EudraCT number 2010-023957-12 885 patients	SCPRT (5 × 5 Gy) followed by Oxaliplatin/capectabine 6 cycles versus Control capecitabine + CRT	MRI-defined entry	Yet to open	CRT 50.4 Gy/28# with capecitabine	Primary endpoint: 3-year DFS
COPERNICUS NCRI stratified phase II NCT01263171 80 patients	Panitumumab/FOLFOX for 4 courses for Kras WT then SCPRT FOLFOX for 4 courses for Kras WT then SCPRT	MRI defined entry	Yet to open	SCPRT for all patients	Primary endpoint: proportion of patients who commence neoadjuvant chemotherapy and radiotherapy and then undergo surgical resection
French phase II NCT00865189 91 patients	FOLFOX + bevacizumab for 6 courses then CRT(with bevacizumab/5FU) versus CRT alone	No	Ongoing not recruiting		Primary endpoint : pCR
Chinese randomised phase II NCT01211210 495 patients	FOLFOX (4 cycles) then surgery versus FOLFOX CRT Versus 5FU CRT (control)	No	Recruiting		Primary endpoint 3-year DFS
SWOG study NCT00070434 Up to 65 patients	Multiple regimens	T4 rectal cancer	Ongoing not recruiting	CRT with capecitabine	Primary endpoint : response
Polish Study NCT00833131 540 patients	SCPRT (5 × 5 Gy) followed by FOLFOX (3 cycles) then surgery versus 5FU/capecitabine CRT (50 Gy) as control	Unresectable rectal cancer	Recruiting	SCPRT versus CRT	Primary endpoint : the rate of R0 resection
Beth Israel Study NCT00831181 22 patients	Six cycles of modified FOLFOX 6 followed by TME followed by an additional six cycles of FOLFOX 6	MRI T3N0M0 or T1–3N1M0	Recruiting		Primary endpoint: pathological response and complete response

Continued on next page

Table 4 – continued

Study	Preoperative treatment	Entry criteria	Status	RT/CRT	Comments
Memorial Sloan Kettering study NCT00462501 36 patients	Neoadjuvant chemotherapy (FOLFOX and bevacizumab) with selective use of radiation for locally advanced rectal cancer	No MRI ERUS only T1N1, T2N1, T3N0 or T3N1 by ERUS	Active not recruiting		R0 resection rate
Japanese study[a] 30 patients	Neoadjuvant chemotherapy (XEOX and bevacizumab)		Recruiting	None	Primary endpoint: treatment compliance Secondary endpoints OS, DFS, local recurrence-free survival, ORR, R0 resection rate and adverse events

NCRI, National Cancer Research Institute; RT/CRT, radiotherapy/chemoradiotherapy; MRI, magnetic resonance imaging; SCPRT, short-course preoperative radiotherapy; pCR, pathological complete response; DFS, disease-free survival; 5FU, 5-fluorouracil; TME, total mesorectal excision; ERUS, endorectal ultrasound; OS, overall survival; ORR, objective response rate.
[a] Ref. [129]

surgery or increasing the interval between CRT and surgery, and allowing more time for response or even administration of two additional cycles of FOLFOX chemotherapy, it may be feasible to increase down-staging and achieve a higher rate of pCR [29,122].

The 'Timing of Rectal Cancer Response to Chemoradiation Consortium' phase II multicentre trial used NACT as consolidation chemotherapy in the interval following CRT prior to surgery, with pCR as the primary endpoint. An initial cohort preserved the standard 6–8 week interval between completion of CRT and surgery, which achieved a pCR of 18%. Sequential cohorts added further cycles of consolidation FOLFOX after CRT prior to surgery, increasing the pCR rates to 25% and 30%, respectively [29]. Postoperative adjuvant FOLFOX chemotherapy was also administered to achieve a total of 6 months of systemic chemotherapy.

The delay in surgery by leaving the primary in situ could potentially increase the chance of metastatic disease. A further question remains as to whether FOLFOX is as effective at preventing metastatic disease if the primary (with presumed stem cells) remains in situ when the chemotherapy is interrupted and attenuated by delivery in a few cycles rather than as a continuous 3–6-month treatment.

5.3. *Neoadjuvant chemotherapy without chemoradiation*

Neoadjuvant chemotherapy may achieve better access to malignant cells when the tumour has an intact blood supply, and may offer better compliance to treatment [116]. Systemic doses of chemotherapy can be delivered at an early stage of the diagnosis rather than after a delay of up to 18 weeks associated with standard CRT. Two studies from the Memorial Sloan-Kettering Cancer Center support the feasibility of neoadjuvant chemotherapy alone in rectal cancer [31,32]. This feasibility study in patients with clinical stage II–III [31] rectal cancer (but not T4 tumours) used FOLFOX (oxaliplatin and 5-flourouracil) with bevacizumab [31] The R0 resection rate was the primary outcome. They reported a pCR in 8/29 patients (27%).

6. Trials in progress (Table 4)

A Polish study (NCT00833131) in unresectable rectal cancer addresses the question of whether SCPRT (25 Gy in 5 fractions) followed by consolidation chemotherapy using FOLFOX4 can increase the rate of R0 resection compared with the standard of conventionally fractionated chemoradiation (50.4 Gy total dose in 28 fractions of 1.8 Gy over 5.5 weeks with FULV or capecitabine).

A similar study (RAPIDO) is a collaboration of Dutch and Swedish study groups and compares chemoradiation followed by delayed surgery and postoperative adjuvant chemotherapy with 5×5 Gy SCPRT followed by chemotherapy and then followed by surgery.

The present authors are participating in a randomised phase II neoadjuvant study (BACCHUS (Bevacizumab and Combination Chemotherapy in Rectal Cancer until Surgery) in resectable rectal cancer where preoperative MRI suggests adverse features such as EMVI, but the CRM is not threatened.

The study aims to evaluate the efficacy, toxicity and feasibility of FOLFOX/ bevacizumab versus FOLFOXIRI/ bevacizumab.

7. The future

Many questions regarding the role of neoadjuvant chemotherapy remain. In CRC, as in other malignancies, combination cytotoxic chemotherapy is more effective in improving survival, so is the current standard of 5FU or capecitabine the optimal partner to radiotherapy in preoperative CRT? Is the theoretical benefit of additional agents such as oxaliplatin outweighed by the increase in acute toxicity, or disguised/diluted by the short-term duration of weeks rather than months and the failure of current regimens to achieve systemically active doses? Is there a role for altered fractionation in conjunction with concurrent chemotherapy? Should we integrate targeted therapies into CRT or will we find antagonism as with the combination of EGFR and VEGF inhibition and chemotherapy? Can we reduce the acute and late toxicity of CRT with improvements in RT delivery such as IMRT/ VMAT?

Finally, is disease stage (i.e. cTN) the best way to select for SCPRT/ CRT treatment? Can we identify patients more or less likely to benefit from preoperative CRT, in terms of defining either patients with a particularly low risk of local recurrence who do not require RT, or patients with a particularly high risk of metastatic disease for whom pelvic RT is probably irrelevant [43].

8. Conclusion

There is strong evidence for the role of radiotherapy in reducing the risk of local recurrence. Radiotherapy remains an important component of the multimodal treatment of rectal cancer, particularly if the CRM is threatened. The two current routinely administered (and evidence-based) different approaches (SCPRT and neoadjuvant CRT) are supported by large randomised phase III trials, and are now endorsed and widely used for resectable rectal cancer (T3–T4 or N+). However, routine use and support for both approaches is not universal. Individual radiation oncologists often favour one or other of these approaches. Arguments usually address the risk of local recurrence, enabling a curative resection and facilitating sphincter-sparing surgery, rather than the integration of systemic chemotherapy and the high risk of metastatic disease. However, CRT has found favour because of the opportunity for response and down-staging and even complete pathological response.

To increase tumour resectability, there is scope for escalating the dose of radiation – particularly to the area where the CRM is threatened on MRI – either with HDRBT or the opportunity for dose-painting with IMRT. For less advanced cases, where the CRM is not threatened, the risk of metastatic disease now predominates over the risk of local recurrence. To reduce metastases, systemically active cytotoxic chemotherapy with or without biological agents is clearly required. Chemotherapy at systemically effective doses is therefore a logical way to improve survival in patients with locally advanced rectal cancer. Concurrent, induction, and consolidation chemotherapy prior to surgery are all potential strategies for improving outcome. Trials are required to assess the role of chemotherapy both with and without radiotherapy.

Increasing surgical precision and a greater recognition of the long-term functional effects of radiotherapy and the risks of second malignancy have reduced local recurrence, and prompted a more selective use of neoadjuvant radiotherapy treatment based on MRI-derived risk. Treatment choices for the individual should now reflect the surgeon's and multidisciplinary team's views on a more realistic balance between the relative importance of preventing local recurrence, the adverse impact of radiotherapy on function and quality of life, the avoidance of a permanent stoma and the more predominant risks of metastatic disease.

In the future imaging and biomarkers will increasingly predict the risk of local recurrence, metastatic disease, and those patients more likely to suffer severe late effects from radiotherapy, and thus help to individualise treatment.

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